Table 4
Multiple Regression Analyses—Factors Correlated with Fatigue

Model	Independent Variable	Coefficient	Standardized Coefficient	Multiple R^2	t	P
Model 1 ($n = 192$)	Psychological distress[a]	0.69	0.48	0.30	8.23	<0.001
	Performance status[b]	−0.14	−0.22	0.10	−3.37	<0.001
	Dyspnea[c]	1.09	0.11	0.03	2.03	0.04
	Appetite loss[d]	1.59	0.15	0.06	2.52	0.01
Dependent variable: fatigue at Time 1, intercept = 19.30, multiple R^2 = 0.50, adjusted R^2 = 0.49						
Model 2 ($n = 129$)	Psychological distress	0.32	−0.20	0.11	2.49	0.01
	Performance status	−0.16	−0.22	0.11	−2.85	<0.01
	Dyspnea	0.92	0.09	0.03	1.27	0.21
	Appetite loss	0.61	0.05	0.02	0.68	0.50
	Fatigue at Time 1	0.45	0.40	0.26	4.56	<0.001
	Interval between Time 1 and Time 2	0.09	0.06	0.00	0.97	0.33
Dependent variable: fatigue at Time 2, intercept = 13.13, multiple R^2 = 0.53, adjusted R^2 = 0.51						
Model 3 ($n = 73$)	Change in psychological distress	0.49	0.32	0.12	3.76	<0.001
	Change in performance status	−0.11	−0.19	0.02	−2.20	0.03
	Change in dyspnea	2.40	0.25	0.05	3.11	<0.01
	Change in appetite loss	−0.01	0.00	0.00	−0.01	0.99
	Fatigue at Time 1	0.70	0.63	0.37	7.53	<0.001
	Interval between Time 1–3	−0.01	−0.12	0.02	−1.46	0.15
Dependent variable: fatigue at Time 3, intercept = 8.58, multiple R^2 = 0.57, adjusted R^2 = 0.54						

[a]Total score of HADS (Hospital Anxiety and Depression Scale).
[b]Defined by Karnofsky criteria.
[c]Assessed using a five-point Likert scale (1 = not at all to 5 = very much).
[d]Assessed using a three-point objective rating (1 = not at all to 3 = over threshold).

patients who suffered from cognitive dysfunction.[30] This problem should be considered in future studies of comparable populations. Another limitation was the use of invalid methods to assess symptoms other than fatigue. No comprehensive symptom inventories that were sufficiently brief and simple to use with severely exhausted patients were available at the time of protocol development.

In conclusion, this study revealed that fatigue in terminally ill cancer patients is closely correlated with both physical and psychological factors and that both of these factors may be closely related to the manifestations of fatigue. More attention to these factors could lead to a better understanding of fatigue in this population. Further research is required to examine whether the management of these factors may be effective for ameliorating fatigue. Also, patient suitability for the application of each mode of treatment should be clarified.

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ORIGINAL ARTICLE

Factors that impede the discharge of long-term schizophrenic inpatients

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Abstract
The aim of the present study was to explore factors that impede the discharge of long-term schizophrenic inpatients, and it was focused on the patients' subjective views. Semi-structured interviews based on the Occupational Self Assessment (OSA) of 73 long-term inpatients with schizophrenia and 24 schizophrenic patients who had been discharged from hospitals after a long-term stay were conducted. Logistic regression analysis was performed. The results revealed that the factors that impeded the discharge of schizophrenic patients from hospitals were advanced age, severe mental symptoms, and higher rating of one's own capabilities in daily living. These results suggest that schizophrenic long-term inpatients require occupational interventions that help patients to have a realistic image of their daily life after discharge and that invite them to update their self-assessments of competence related to the skills needed for daily life.

Key words: *Competence, Model of Human Occupation, Occupational Self-Assessment, occupational therapy*

Introduction

There is increasing awareness in society of the need to promote the social activity of mentally ill individuals in local communities by increasing facilities that assist them to resume social activities and by improving and expanding regional support services for them. As a result of this trend, both the numbers of patients admitted to and discharged from psychiatric hospitals have been increasing, and the mean hospital stay of such patients has gradually been becoming shorter. However, we must acknowledge that quite a few factors still make it difficult for schizophrenic patients to be discharged from hospitals where they have resided for prolonged periods.

Why is it difficult for long-term hospitalized patients to be discharged from hospitals? Several studies have attempted to identify factors that impede the discharge of long-term schizophrenic inpatients (1–5). Howat (1) identified gender as a factor associated with degree of difficulty of discharge. Babiker (2) pointed out social factors (low probability of becoming employed after discharge, and lack of social support) as being responsible for

the long-term hospital stays of these patients. However, most studies on factors that impede the discharge of schizophrenic patients have been based on analyses of objective factors (e.g. profiles of individual patients and basic background factors of the patients) (6–9), and none has involved analysis of subjective factors, e.g. the views of long-term hospitalized patients concerning their current status and environment or the characteristics of such views. The International Classification of Functioning, Disability and Health (ICF) (10) emphasizes the overall daily living functions and disabilities of individual patients, including the dimensions of self and subjective views. Theories proposed in regard to occupational therapy (OT) have also attached importance to volition of individual clients and problem-dealing methods tailored to individual clients (11,12). Therefore, when analyzing factors that impede the discharge of long-term schizophrenic inpatients, it seems essential to explore such factors by analyzing the views of individual patients. If problems inherent in individual patients that impede their discharge are explored by analysis of their subjective views, it should be possible to find an

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important suggestion for occupational therapy intervention for long-term schizophrenic inpatients.

The aim of this study was to explore factors that impede the discharge of long-term schizophrenic inpatients by focusing on their subjective views. To this end, the views of their current status of long-term schizophrenic inpatients and schizophrenic patients who had been discharged after a long-term hospital stay were compared with the goal of identify the characteristics of long-term hospitalized patients and quantitatively analyzing factors that impede their discharge. In view of a report that the mean hospital stay of Japanese patients on psychiatric wards is 373.9 days, in this study "long-term stay" was defined as one year or more.

Material and methods

Subjects

We obtained approval for the study from the 3 psychiatric hospitals in Japan. All participants were permitted by the attending physician to participate in this study.

(1) Long-term inpatients (long-term stay group). The subjects were schizophrenic inpatients staying in their current hospital for one year or longer. Of the 93 patients who satisfied the inclusion criteria, 20 refused to answer the questionnaire, and the remaining 73 patients (54 males and 19 females, mean age 57.8 ± 9.15 years) were included in the analysis.

(2) Patients discharged after a long-term hospital stay (discharged group). The subjects were schizophrenic patients receiving psychiatric day care services at facilities affiliated with the above three hospitals, and who were discharged from hospital after a stay of one year or longer. Of the 33 patients who satisfied the inclusion for the discharged group, 9 refused to answer the questionnaire, and the remaining 24 (19 males and 5 females, mean age 45.5 ± 12.0 years) were included in the analysis.

The most common reasons for refusal were "I don't want to participate" and "I am not interested", but some patients refused to participate because of being in a poor physical condition.

Data collection

Data were collected through a semi-structured interview using a questionnaire. The interviews were carried out on individual subjects in a room familiar to them, and only the interviewer and the subject were in the room. Because the questions in the questionnaire were written in simple but somewhat abstract words, the interviewer explained the meaning in order to standardize the interpretation of the questions. As a rule, the questionnaire was handed directly to the subject and filled out by the subject. The questionnaire was filled out by the interviewer if the subject could not read the questions or was visually disabled. The interview was performed by one of the authors (YI).

Measures

(1) Background data. Background data (age, gender, marital status, educational history, occupational history, marriage status, number of hospital stays, duration of total hospital stay, and dosage of antipsychotic drugs) were collected from the medical records of each subject.

(2) Positive and Negative Syndrome Scale. The Positive and Negative Syndrome Scale (PANSS) was developed and standardized by Kay et al. to assess the severity of the symptoms of schizophrenia (13), and severity is scored from 1 (absent) to 7 (most severe). The higher the score, the more severe the symptom is. This scale scores 30 symptoms (7 positive symptoms, 7 negative symptoms, and 16 general psychopathological symptoms). Scoring is based on the subject's statements during an interview, on observations, and on information obtained from medical staff. In this study the scores for the 16 general psychopathological symptoms were used to evaluate the subjects. Possible scores ranged from 16 to 112.

(3) Occupational Self-Assessment. The Occupational Self-Assessment (OSA) scale (14) was prepared by a development team composed of Kielhofner and others as a means of assessing clients' self-perception of occupational functioning level and the influence of environments on their functioning. It is a comprehensive self-assessment scale based on a model of human occupation (MOHO) (15) and the concepts of client-centered practice (11,12), which makes it possible to identify problems related to the subject's daily life by understanding subjective views. The validity and reliability were confirmed by Kielhofner et al. (14).

This scale is composed of 29 statements. Part 1 pertains to assessment of "myself" and consists of 21 statements in plain language about occupational behavior. The 21 statements are divided into three subsystems based on the MOHO: "mind–brain–body performance", "habituation", and "volition."

The "mind–brain–body performance" subsystem consists of 11 statements and involves elements such as exercise, processing, communication, and exchange. The "habituation" subsystem consists of five statements and involves elements related to maintenance of daily life patterns such as habits and roles. The "volition" subsystem consists of five statements and involves elements related to one's attitude toward matters such as personal causation, value, and interest.

Subjects self-assess the degree to which each of these 21 statements applies to them. First, subjects rate their *competence* in regard to each statement on a three-point scale, ranging from 1 (I have a problem doing this) to 3 (I do this well). Subjects then rate the *values [values/myself]* of each of the 21 statements to their daily life on a three-point scale, ranging from 1 (This is unimportant to me) to 3 (This is important to me). The gap between competence and value scores is calculated, and defined as degree of *satisfaction [satisfaction/myself]*, ranging from -2 to $+2$.

Part 2 pertains to assessment of "my environments" and consists of eight statements pertaining to physical and social environments. First, subjects self-assess *environmental support* by rating each of the eight statements on a three-point scale from 1 (This is a problem) to 3 (This is very good). Then, *values [values/environment]* and *satisfaction [satisfaction/environment]* related to the environments are self-assessed by subjects, in the same way as described in Part 1.

The statement "taking care of others for whom I am responsible" in Part 1 was excluded from this study, because the subjects were long-term inpatients and had few opportunities to be responsible for other persons. As a result, 28 statements (20 in Part 1 and 8 in Part 2) were used in the evaluation.

Data analysis

The Mann–Whitney U-test and chi-squared test were employed to compare background variables and mental symptoms in the long-term stay group and the discharged group.

To identify factors that impede the discharge of long-term schizophrenic inpatients we used the chi-squared test or the Mann–Whitney U-test (univariate analysis) to compare background variables, mental symptoms, and OSA results (competence, values/myself, satisfaction/myself, environmental support, values/environment and satisfaction/environment) between the long-term stay group and the discharged group. We then used logistic regression analysis by the forced entry method with presence/ absence of discharge as the dependent variable and factors shown to be associated in the univariate analysis as independent variables. If the logistic regression analysis revealed any OSA results to be an associated factor, the subsystems of those statements were compared between the long-term stay group and the discharged group.

The p-values in all tests were two-tailed, and p-values of <0.05 were considered statistically significant. The Statistical Package for the Social Sciences (SPSS) version 14.0J was used for all statistical analyses.

Results

The univariate analysis revealed significant differences between the long-term stay group and the discharged group in regard to age ($p < 0.01$), duration of hospital stay ($p < 0.01$), PANSS ($p < 0.01$), occupational history ($p = 0.12$), competence according to the OSA ($p < 0.01$), and the degree of satisfaction with their environments ($p = 0.04$) (Table I). The logistic regression analysis (forced entry method) with each associated factor revealed in the univariate analysis as an independent variable and presence/absence of discharge as the dependent variable revealed only age ($p < 0.01$) and PANSS ($p < 0.01$) as significantly associated with discharge from hospital (Table II).

Because a close association was found between age and PANSS, we conducted an analysis in which each of these two factors was used separately as an independent variable and the results of OSA were used as another independent variable. The logistic regression analysis with age and the OSA results as independent variables revealed only age to be a significant factor associated with hospital discharge ($p < 0.01$) (Table III). Thus, age was shown to be a factor that strongly influenced patient discharge from hospital. The logistic regression analysis with PANSS and the OSA results as independent variables revealed competence ($p < 0.05$) as well as PANSS ($p < 0.01$) to be significantly associated with discharge (Table IV).

We then compared the results for subjects' competence on the OSA in the long-term stay group and discharged group by the Mann–Whitney U-test, and the results showed significant inter-group differences in the responses to the following statements: "physically doing what I need to do", "taking care of the place where I live", "taking care of myself", "accomplishing what I set out to do", "having a satisfying routine", and "effectively using my abilities" (Table V).

Table I. Comparison between the hospital long-stay group and the discharged group.

		Long-term stay group ($n=73$)	Discharged group ($n=24$)	p^1
Age	Years	57.67 (9.15)*	45.54 (12.02)*	<0.01
Gender	Male	54	19	0.79
	Female	19	5	
Marital status	Yes	12	4	1.00
	No	61	20	
Educational history	≥Junior high	39	16	0.34
	<Junior high	34	8	
Occupational history	Yes	43	21	0.01
	No	30	3	
Marital status	Yes	4	1	1.00
	No	69	23	
Number of hospital stays	Times	4.85 (4.18)	6.96 (7.15)	0.55
Duration of total hospital stay	Days	5438.88 (3874.98)	1473.96 (1706.48)	<0.01
Dosage of antipsychotic drugs	mg	562.43 (440.94)	602.40 (672.96)	0.49
PANSS[2]		39.77 (8.75)	33.50 (6.63)	<0.01
OSA[3]				
Competence		46.21 (7.02)	42.33 (5.90)	0.01
Values/myself		50.95 (6.95)	50.54 (6.29)	0.63
Satisfaction/myself		−4.74 (7.51)	−8.21 (7.57)	0.05
Environmental support		17.22 (3.36)	16.92 (2.08)	0.59
Values/environment		20.29 (3.12)	21.25 (2.36)	0.27
Satisfaction/environment		−3.07 (3.35)	−4.33 (2.88)	0.04

Notes: [1]Mann–Whitney U-test, chi-squared test; [2]Positive And Negative Syndrome Scale; [3]Occupational Self-Assessment. *Average (SD).

Table II. Factors impeding the discharge of long-term schizophrenic inpatients in the logistic regression analysis.

Independent variable	Estimate (beta)	SE	OR	95% CI	p-value
Age	−0.136	0.037	0.873	0.81–0.94	<0.01
Occupational history	1.206	0.796	3.340	0.70–15.90	0.13
PANSS	−0.145	0.048	0.865	0.79–0.95	<0.01
OSA; competence	−0.070	0.054	0.933	0.84–1.04	0.19
OSA; satisfaction/environment	−0.083	0.100	0.920	0.76–1.12	0.40

Table III. Predicted OSA factors that impede discharge (with age).

Independent variable	Estimate (beta)	SE	OR	95% CI	p-value
Age	−0.105	0.027	0.901	0.85–0.95	<0.01
OSA; competence	−0.071	0.044	0.932	0.86–1.02	0.10
OSA; satisfaction/environment	−0.051	0.093	0.950	0.79–1.14	0.59

Table IV. Predicted OSA factors that impede discharge (with PANSS).

Independent variable	Estimate (beta)	SE	OR	95% CI	p-value
PANSS	−0.096	0.034	0.909	0.85–0.97	<0.01
OSA; competence	−0.083	0.042	0.921	0.85–1.00	<0.05
OSA; satisfaction/environment	−0.060	0.080	0.942	0.81–1.10	0.45

Discussion

The response rate was 78.5% (73 out of 93) in the long-term stay group and 72.7% (24 out of 33) in the discharged group. The most common reasons for refusal were "I don't want to participate" and "I am not interested". The refusal by these patients seems to have reflected negative symptoms (e.g. reduced volition and emotional flattening), and it was also

Table V. Comparison of OSA competence items scores.

	Long-term stay group ($n = 73$)	Discharged group ($n = 24$)	p^1
Physically doing what I need to do	2.30 (0.59)*	1.96 (0.75)*	0.04
Taking care of the place where I live	2.26 (0.73)	1.83 (0.82)	0.02
Taking care of myself	2.33 (0.63)	1.92 (0.58)	<0.01
Accomplishing what I set out to do	2.38 (0.62)	2.08 (0.65)	0.05
Having a satisfying routine	2.25 (0.76)	1.79 (0.66)	<0.01
Effectively using my abilities	2.18 (0.69)	1.79 (0.66)	0.02

Notes: [1] Mann–Whitney U-test. *Average (SD).

assumed that some patients refused because of feeling tense when facing the examiner, whom they had never met before. Pinkham (16) reported that schizophrenic patients had impaired interpersonal skills, and this seems to influence the refusal by the participants of this study. Barker (2) recruited familiar nurses to accompany the investigators to reduce patients' mental stress in relation to the questionnaire. The possibility that the inability to include these patients in the study caused some bias cannot be ruled out. When conducting surveys on schizophrenic patients, it seems necessary to minimize tension when the subject is facing the examiner and to adopt a less stressful method of conducting the survey, although it would not be easy to achieve these goals.

The present study attempted to explore factors that impede the discharge of long-term schizophrenic inpatients, by using the OSA to compare a long-term stay group with a discharged group. The results revealed two variables, age and mental symptoms, as factors that significantly impeded the discharge of patients from hospitals. Patients with severe mental symptoms require inpatient treatment, making it difficult for them to return to their local communities. Aging is sometimes associated with problems such as physical complications and reduced physical strength and stamina. Aging is also associated with an increase in the frequency of negative symptoms, such as emotional flattening and reduced volition (17–19). The results of the present study seem to be a good reflection of the characteristics of both long-term inpatients and discharged patients.

The analysis of the results of the OSA showed that the long-term stay group had higher self-ratings of competence and greater satisfaction with their environment than the discharged group. This suggests that the long-term stay group tended to be satisfied with their environment (within the hospital) and to rate their competence higher, while the discharged group tended to be less satisfied with their environment (outside the hospital) and to rate their competence as insufficient. The logistic regression analysis revealed that self-rating of competence, as well as mental symptoms, was a significant factor associated

with hospital discharge. This means that patients who rate their occupational competence higher are less likely to be discharged. A review of the statements on the OSA that showed significant differences in competence rating between the long-term stay group and discharged group revealed that competence rating for the following four statements regarding mind–brain–body performance was significantly higher in the long-term stay group: "physically doing what I need to do", "taking care of the place where I live", "taking care of myself", and "accomplishing what I set out to do." Among the habituation subsystem statements, the competence rating for "having a satisfying routine" was significantly higher in the long-term stay group. Among the volition subsystem statements, the competence rating for "effectively using my abilities" was significantly higher in the long-term stay group. Thus, the competence ratings in regard to six statements were higher in the long-term stay group. Because the scope of activities in hospitals is narrower and many aspects of daily living (meals, healthcare, nursing, etc.) are taken care of by hospital workers, daily living in hospital requires lower levels of competence than daily living in local communities, which requires individuals to take care of everything by themselves. The higher competence rating made by the long-term stay group may be attributable to these differences. With regard to the degree of satisfaction with their environment, it has been reported that both patients and hospital staff tend to view hospitals as protective shelters for patients rather than as places to which patients are committed (20). It has also been reported that patients' degree of satisfaction with the care provided in psychiatric hospitals increases with age (21). The results of the present study corroborate the findings in these previous reports.

The present study revealed that long-term schizophrenic inpatients tend to view themselves as being sufficiently competent to lead their daily lives within the hospital setting and that they tend to be satisfied with their daily lives in the hospital. This finding indicates the need for intervention by occupational therapy approaches that help patients to maintain

images of their daily lives after discharge and that invite them to update their self-assessments regarding competence related to the skills needed for their daily life activities, instead of interventions that focus on daily life within the protective hospital environments alone. To do that, it is necessary to help these patients to have a clear image of their daily life after discharge (e.g. supplying information about social resources available to them, etc.), to talk with the patients about obstacles encountered in their daily life outside hospital (cooking, shopping, finances, etc.), and to seek ways to resolve these issues together. The present study focused on the subjective views of long-term schizophrenic inpatients with regard to their current status and provided clues to concrete occupational therapy approaches that should be useful for long-term schizophrenic inpatients. The results of this study suggest that occupational therapists can play a significant role in facilitating resumption of social activity in the community by long-term schizophrenic inpatients.

This study had several limitations. First, it was confined to patients in psychiatric hospitals alone and did not cover all long-term schizophrenic inpatients. Since the environments of long-term inpatients may vary among hospitals, it is necessary to determine whether the findings in this study are valid in other facilities. Second, this study was designed to identify factors that impede the discharge of schizophrenic patients by comparing long-term inpatients with patients discharged after a long-term stay. It would be desirable to conduct a follow-up study that focused on changes in the views of long-term schizophrenic inpatients regarding their current status and their relationship to the degree of difficulty of discharge, with the goal of more precisely identifying factors that impede their discharge from hospitals.

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Short Communication: Psychological impact and associated factors after disclosure of genetic test results concerning hereditary non-polyposis colorectal cancer

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Summary

The purpose of this study is to elucidate the psychological impact of disclosure of genetic test results concerning hereditary non-polyposis colorectal cancer (HNPCC) and to assess factors associated with it, with particular focus on memory function. The subjects were persons who were suspected of having HNPCC and given the choice of undergoing genetic testing. The post-genetic testing psychological impact was evaluated by means of the Impact of Event Scale-Revised (IES-R), and personality tendencies and memory function were evaluated. Final data were obtained from 46 subjects. The results of the genetic testing were 'mutation-positive' in 18 subjects, 'uninformative' in 18 subjects, and 'mutation-negative' in 10 subjects. Comparison of the IES-R scores showed that they tended to be higher in the mutation-positive group, but the differences were not statistically significant. The personality tendency 'nervousness' and verbal memory assessed prior to disclosure were significantly associated with total score on the IES-R. Based on the results of this study it seems possible to minimize the risk of a psychological impact of disclosure of genetic test results by reassessing the follow-up system for persons at high risk of a psychological impact. Copyright © 2008 John Wiley & Sons, Ltd.

Key Words

cancer; genetic testing; HNPCC; memory function; psychological impact

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Introduction

Advances in genetics in recent years have made major contributions to the development of medical genetics. The existence of 'familial

tumours' has been recognized, and genetic testing is now being attempted and has the potential to be of incalculable benefit to humanity (Offit, 1998). Numerous gene analyses related to the genesis and development of colorectal cancer have been conducted, and the existence of hereditary colorectal tumours in the form of hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis has been identified.

However, in contrast to the advances in genetic techniques there has been a great deal of apprehension in regard to the psychological factors associated with their application (Offit, 1998). For this reason some recent studies have investigated the psychological aspects of undergoing genetic testing for hereditary colorectal tumours, especially HNPCC, and being informed of the results (Aktan-Collan, Haukkala, Mecklin, Uutela, & Kääriäinen, 2001; Codori et al., 2003; Esplen et al., 2001; Gritz et al., 2005; Murakami et al., 2004), and many of the studies have shown that genetic testing does not result in short- or long-term adverse psychological outcomes, including depression or anxiety.

Some studies that have investigated the psychological aspects of genetic testing in recent years have been conducted from the standpoint of post-traumatic stress disorder (PTSD; Claes, Denayer, Evers-Kiebooms, Boogaerts, & Legius, 2004; Meiser et al., 2004). PTSD develops as a result of exposure to a traumatic event, and the sensitivity and vulnerability of the individual to stress are considered factors in its aetiology. PTSD is manifested by a decline in ability to concentrate and remember, and since hippocampal atrophy has been observed on diagnostic images in a high percentage of patients clinically, interest has increased in the parenchymal factors that underlie the symptoms. There have been particularly numerous reports of studies on PTSD and decreased memory function (Bremner et al., 1993; Golier et al., 2002; Lindauer, Olff, van Meijel, Carlier, & Gersons, 2006). While reduced memory function has been reported in PTSD in many prior studies, some reports claim that the hippocampal damage reflects stress vulnerability before the traumatic experience, while others claim that it develops as a result of traumatic experiences or PTSD. As a result of these conflicting findings, whether the hippocampal damage is a cause or a result remains unclear. Furthermore, hardly any studies have attempted to identify factors, especially biological factors, which are

associated with the psychological effects of being informed of the results of genetic testing for HNPCC.

The purpose of the present study was to investigate the psychological impact of disclosure of genetic test results and the factors associated with it, especially focusing on memory function, in subjects who underwent genetic testing for HNPCC and were informed of the results.

Methods

Subjects

The subjects were persons who fulfilled the following eligibility criteria amongst those examined for the first time in the genetic counselling outpatient clinic of the National Cancer Center Hospital in Japan: (1) HNPCC was suspected based on a survey that included a pedigree chart, and the choice of undergoing genetic testing was offered and (2) 20 years of age or more.

Subjects to whom the following factors applied were considered ineligible, and they were excluded: (1) subjects for whom it was difficult to understand the purpose of the study (dementia, etc.), (2) subjects in serious physical condition and (3) subjects from families in which the proband was unknown.

Measures

Sociodemographic variables. Information regarding the interval between genetic counselling and the disclosure of the test results, age at the time of the examination, gender, marital status, whether the subject had children, history of cancer, household size, occupation, education level, and whether the subject had a religious faith was collected by means of a questionnaire.

Psychological impact. We used the revised version of the Impact of Event Scale (IES-R; Asukai et al., 2002; Horowitz, Wilner, & Alvarez, 1979), which evaluates the effect of psychological trauma. It is a self-report questionnaire devised by Weiss and Marmar (1997) and consists of 22 items. The IES-R is composed of three subscales, that is, a hyperarousal subscale in addition to the previous intrusion subscale and avoidance subscale.

Personality characteristics. We used the Eysenck Personality Questionnaire-Revised (EPQ-R) to assess personality characteristics. The EPQ-R is a self-report questionnaire prepared by Eysenck and Eysenck (1985) and consists of 48 items that evaluate personality traits. It is composed of four scales: Psychoticism, Neuroticism, Extraversion or Introversion and Lie.

Memory. We used the revised version of the Wechsler Memory Scale (WMS-R) to assess memory. The original WMS was developed as a scale to objectively measure memory function (Wechsler, 1981). WMS-R measures four memory functions: verbal memory, visual memory, attention or concentration and delayed memory, but only verbal memory and visual memory were evaluated in this study. Since a reduction in hippocampal volume in the brain had been described in PTSD in the past (Bremner, 1999), and the decrease in hippocampal volume has been reported to be associated with a decrease in memory function (Sass et al., 1990), we measured memory function as a means of evaluating hippocampal function.

Evaluation procedure

This study was approved by the Institutional Review Board of the National Cancer Center Hospital of Japan.

After the completion of genetic counselling, the physician in charge of the study explained the nature of the study according to the disclosure document to the potential subjects who fulfilled the eligibility criteria. Those who gave their consent were assessed in regard to socio-demographic variables, personality traits and memory function before disclosure of the genetic rest results, and that information was used as the baseline data. The IES-R was administered as a measurement of psychological impact 1 month after explanation of the genetic test results, and the scores were used as the data 1 month after disclosure of the test results.

Statistical analysis

The data were not normally distributed, so non-parametric tests were used.

The Kruskal-Wallis test was performed in regard to each of the items that evaluated psycho-logical impact in order to conduct a comparative assessment between groups classified according to the results of the genetic test.

Spearman's rank correlation coefficient, the Mann-Whitney U-test, or the Kruskal-Wallis test was used to assess the factors associated with degree of psychological impact, and the IES-R scores and other factors were analysed for associations.

The p values in all of the tests are two-tailed, and $p < 0.05$ were considered significant. Statistical Package for the Social Sciences software version 14.0J for Windows was used to perform all of the statistical analyses.

Results

Subjects' participation

Eight potential subjects were ineligible because they refused to undergo genetic testing, or it was difficult for them to understand the purpose of the study, or the proband was unknown. There were 51 potential subjects who fulfilled the eligibility criteria, and consent to participate in the baseline survey was obtained from 47 of them. One of the 47 subjects later refused to take the memory function test (WMS-R), and ultimately there were 46 subjects of the final analysis.

Subjects' characteristics and results of genetic testing

The socio-demographic variables, results of genetic testing, and scores on the EPQ-R of the 46 subjects who met the eligibility criteria are shown in Table I. The results of the genetic testing were 'mutation-positive' in 18 (39.1 per cent) subjects, 'uninformative' in 18 (39.1 per cent) subjects and 'mutation-negative' in 10 (21.7 per cent) subjects.

Psychological impact of the results of genetic testing

The scores on the IES-R, the scale that was used to evaluate degree of psychological impact in this study, are shown in Table II.

The IES-R scores tended to be higher in the mutation-positive group than in either of the other two groups, but the differences were not statistically significant.

Table I. Subjects' characteristics ($n = 46$).

	n	Mean	SD
Age		49.5	13.0
Gender			
Male	22		
Female	24		
Number of days after receipt of		78.7	48.8
the test results			
Marital status			
Married	38		
Unmarried	8		
Children			
Yes	37		
No	9		
History of cancer			
Unaffected	14		
Affected	32		
Proband			
Yes	29		
No	17		
Household size			
Alone	4		
≥ 2	42		
Employed			
Yes	32		
No	14		
Education			
≤ 12	187		
>2	28		
Religion			
Yes	7		
No	39		
Genetic testing results			
Positive	18		
Uniformative	18		
Negative	10		
EPQ-R			
Psychoticism		3.4	1.7
Neuroticism		4.4	2.5
Extraversion/Introversion		6.6	3.3
Lie		5.5	3.0
WMS-R			
Verbal memory		100.5	12.5
Visual memory		118.3	12.1

EPQ-R: Eysenck Personality Questionnaire-Revised; WMS-R: Wechsler Memory Scale-Revised.

Factors associated with psychological impact

The results of a univariate analysis showed that 'neuroticism' on the EPQ-R ($p = 0.010$) and 'verbal memory' on the WMS-R ($p = 0.037$) were significantly associated with total IES-R scores, which are an indicator of psychological impact.

Table II. Comparison of psychological impact between groups that were classified on the basis of the genetic test results.

	Positive	Negative	Uninformative	p^*
IES-R				
Intrusion	28.33[†]	19.70[†]	20.78[†]	0.085
Avoidance	25.75	21.95	22.11	0.385
Hyperarousal	25.67	22.39	21.60	0.512
Total	28.78	19.44	21.30	0.070

* Kruskal-Wallis test, [†] Mean rank.
IES-R: Impact of Event Scale-Revised.

No significant associations were found with any other factors (Table III).

Discussion

Factors associated with the psychological impact of the disclosure of genetic information

Personality tendencies; neuroticism. The results of the analysis in this study showed that 'neuroticism' was significantly associated with greater psychological impact of disclosure of the genetic information. Previous studies have reported that neurotic, highly anxious and depressive personalities are the factors associated with psychological impact the results of this study supported the results of the studies of Tjemsland, Soreide and Malt (1998) Neuroticism is anxiety proneness, and hence we would expect persons who are more anxiety prone to be more prone to react to the threat of testing or the results of testing.

Memory function; verbal memory. A significant association was found between the psychological impact of disclosure of genetic information and verbal memory. Bremner et al. (1993) observed verbal memory impairment in a study of PTSD patients amongst American soldiers returning from combat in Vietnam. The same as in these earlier studies, the results of the present study support an association between psychological impact and memory disturbances, particularly verbal memory disturbances.

Knowledge of the pathology underlying PTSD and memory disorders has accumulated, and nervous system damage, primarily to the hippocampus, has been postulated in PTSD. The question of whether the memory disorder in PTSD

Table III. Factors associated with psychological impact (total score on the IES-R).

		r	p*
Age		−0.11	0.458
Number of days after receipt of the test results		−0.103	0.496
EPQ-R			
Psychoticism		−0.069	0.647
Neuroticism		0.377	0.010
Extraversion/Introversion		−0.189	0.210
Lie		−0.006	0.969
WMS-R			
Verbal memory		−0.308	0.037
Visual memory		−0.172	0.254

	n	Mean	p†
Gender			
Male	22	21.57	0.320
Female	24	25.27	
Marital status			
Married	38	23.62	0.890
Unmarried	8	22.94	
Children			
Yes	37	23.11	0.669
No	9	25.11	
History of cancer			
Unaffected	14	23.07	0.879
Affected	32	23.69	
Proband			
Yes	29	23.86	0.799
No	17	22.88	
Household size			
Alone	4	21.00	0.678
≥2	42	23.74	
Employed			
Yes	32	23.97	0.703
No	14	22.43	
Education			
≤12	18	23.78	0.905
>2	28	23.32	
Religion			
Yes	7	30.57	0.107
No	39	22.23	

	n	Mean	p‡
Genetic testing results			
Positive	18	28.78	0.070
Uninformative	18	19.44	
Negative	10	21.30	

* Spearman's rank correlation coefficient, † Mann-Whitney U-test, ‡ Kruskal-Wallis test.

patients is due to the PTSD, or whether persons who already have a memory disorder tend to develop PTSD has been debated, but no clear answer has been obtained. The finding of a significant association between the strength of the psychological impact after disclosure of the genetic information and poor memory function before disclosure of the genetic information in the present study suggests that the poorer a person's memory function is originally, the more susceptible the person is to a psychological impact. In other words, it was suggested that damage to the hippocampus existed before the traumatic experience, and that the traumatic experience in such individuals, and their vulnerability to stress, that is, the problem of dealing with the stress associated with it, governed the severity of the psychological impact on them.

Limitations and perspectives

The first limitation of this study that can be cited is that since the subjects were persons who accepted the offer of genetic testing and genetic counselling, it would be difficult to claim that the subjects of this study adequately represented the parent population. The second limitation is that we used scales that measure psychological impact and made measurements that especially focused on PTSD. It seems that in the future it will also be necessary to evaluate other psychological parameters, such as depression, cancer worry and cancer-specific distress. Lastly, as the present study elucidated, only the short-term effects of disclosure of the results of genetic testing and the sample size was small, it cannot be concluded that there was no significant difference between IES-R scores according to mutation status groups. In order to determine the full psychosocial impact of genetic testing it will be necessary to extend the investigation to assessment of its long-term effects.

Despite the existence of these limitations, the results of this study suggest that the risk of a psychological impact of disclosure of genetic test results can be minimized by reviewing the counselling system for subjects who have neuroticism or a verbal memory disturbance.

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Psychosocial factors and survival after diagnosis of inoperable non-small cell lung cancer

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Abstract

Objective: Although several previous studies have investigated the association between psychosocial factors and the survival of lung cancer patients, most previous studies were flawed by severe methodological limitations. The purpose of the present study was to use a rigorous study design to investigate the association between relevant psychosocial factors and survival after a diagnosis of inoperable non-small cell lung cancer (NSCLC).

Methods: The subjects were 122 consecutive newly diagnosed patients with inoperable NSCLC. Patients coping with cancer, psychological distress, clinical depression, and social support were evaluated after diagnosis but before treatment and 2 months later. After a 2-year follow-up period, 108 patients had died. The survival data were censored for the remaining 14 patients. The influence of psychosocial factors after diagnosis but before treatment on survival time was analyzed using a Cox regression, with adjustments for well-established (definite and/or possible) prognostic factors. The stability of the investigated psychosocial factors was also examined.

Results: None of the examined psychosocial factors significantly predicted survival time among the patients with inoperable NSCLC. Among the biomedical factors that were examined, advanced clinical stage, a high serum lactate dehydrogenase level, and not receiving chemotherapy were independently associated with shorter survival periods. Most of the psychosocial factors exhibited a moderate to high stability.

Conclusions: We found little convincing evidence that psychosocial factors after cancer diagnosis had a clinically relevant effect on the survival of inoperable patients with NSCLC. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: coping; social support; survival; cancer; oncology

Introduction

There is much interest in the association between the mind and body, and this is not exceptional in oncology settings, possibly because cancer is a potentially life-threatening disease and is often accompanied by major psychological distress. Actually, many professionals and the lay public believe that psychosocial factors play a major role in cancer onset and its progression [1,2]. On the other hand, although several previous studies have investigated the effects of psychosocial characteristics (including personality, coping, general psychological distress, depression, and social support) on survival, the influence of psychosocial factors on the survival of cancer patients remains controversial [1,3–5].

Lung cancer is the most common type of cancer and the most common cause of cancer-related death in the world [6,7]. In Japan, lung cancer is the leading cause of death from cancer among men, and the incidence of lung cancer has been increasing in recent years [8]. In a study examining psychological distress and its relation to the site of cancer, primary lung cancer was strongly associated with psychological distress in cancer patients [9]. In addition, several previous studies have demonstrated that the highest prevalence of psychological distress was observed among patients with lung cancer [10,11]. Our previous study indicated that 19% of advanced lung cancer patients experienced diagnosable anxiety/depression between the time of diagnosis and initial treatment and that 35% of them continued to experience the same disorder for at least 6 months after diagnosis [12]. Thus, in general, psychological distress is highly prevalent among lung cancer patients; consequently, these psychosocial issues should not be neglected.

Several previous studies have investigated the association between lung cancer patient's psychosocial factors and survival. For example, Faller et al. reported a significant association between depressive coping/interviewer-rated emotional distress and a shorter survival period [13–15]. Nakahara et al. also demonstrated a significant association between mental state, as assessed using an egogram, and survival [16]. Other groups have reported significant associations between survival and depression [17], suicidal ideation [17], personality [18], psychosocial well-being [19], social support [19], and symptom distress [20], although some studies failed to clarify a significant influence of factors such as marital status [21], depression [15,22], social support [21], 24-h urinary cortisol level (used as an indicator of physiological or psychological stress) [23], self-reported psychological distress [13,14,20], and concerns [20]. On the other hand, most of these previous studies were flawed by severe methodological limitations, including a retrospective design [18,20], a short or unclear follow-up period (e.g. less than 1 year) [17,18], a small sample (e.g. less than 100 patients) [17,20], the lack of controls for well-established prognostic factors (especially because several biomedical factors have been identified as definite/possible prognostic factors among patients with non-small cell lung cancer (NSCLC) [24], and adjustments for these biomedical factors should be performed when evaluating other prognostic factors [25]) [13,14,18,20], and the assessment of variables after treatment (psychosocial factors should be evaluated at the same time as other biomedical factors, before treatment) [18,20]. In addition, none of the previous studies checked the stability of the investigated variables, although many psychosocial factors can change during the course of a patient's illness, and none of the studies simultaneously investigated a broad range of psychosocial factors, including diagnosable depression—known to be the most common psychiatric disorder, using a reliable measure, such as a structured clinical interview.

The purpose of the present study was to use a more rigorous study design to investigate the association between relevant psychosocial factors and patient survival after a diagnosis of inoperable NSCLC.

Patients and methods

Patients

The subjects were consecutive patients with NSCLC who had been newly diagnosed at the Thoracic Oncology Division, National Cancer Center Hospital East (NCCHE), Japan, between August 1996 and January 1998. Patients were included in the study if they met all of the following criteria: (1) histologically or cytologically confirmed NSCLC; (2) diagnosis of unresectable cancer (clinical stage unresectable IIIA, IIIB, or IV); (3) informed of their lung cancer diagnosis; (4) a performance status (PS) of between 0 and 2, according to the Eastern Cooperative Oncology Group criteria; (5) follow-up care at the Thoracic Oncology Division of the NCCHE; (6) 18 years of age or older; (7) not too ill to participate in an interview or complete questionnaires; (8) absence of brain metastasis, as confirmed using brain CT or MRI; (9) ability to provide written consent; (10) absence of cognitive impairment, such as delirium or dementia (if a subject was suspected of having a cognitive impairments, cognitive function was evaluated using the Mini Mental State Examination (MMS); only subjects with an MMS score of 24 or more were allowed to participate in the study [26]); (11) no history of previous anticancer treatment within 5 years; and (12) no active concomitant cancer.

This study was approved by the Institutional Review Board and the Ethics Committee of the National Cancer Center of Japan and was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each subject before enrollment into this study.

Assessment of psychosocial factors

We investigated each patient's coping with cancer, psychological distress, psychiatric disorders, and social support as potential psychosocial predictors of survival. These factors, other than the psychiatric disorders, were evaluated twice (after diagnosis but before treatment: baseline (T1), and 2 months after T1; T2) to check the stability of the factors. An assessment of psychiatric disorders was not conducted at T2 to avoid unnecessary increases of the patient's burden. The measures at baseline were investigated as potential prognostic factors.

Coping with cancer

Each patient's coping with having cancer was measured using the Japanese version of the Mental Adjustment to Cancer (MAC) scale [27]. The MAC scale consists of five subscales. Our previous study revealed that the Japanese version of the MAC scale was valid and reliable [27]. Among the subscales, we used fighting spirit and helplessness/hopelessness, which were shown to be potential prognostic factors in a previous study [28].

Psychological distress

Psychological distress was evaluated using the Profile of Mood States (POMS) [29]. The POMS is a 65-item self-rated scale for measuring mood

disturbance. The POMS is a widely used, reliable measure of emotional distress that has been validated in cancer patients and demonstrated to be reliable for Japanese people [30]. The Total Mood Disturbance (TMD) scale of the POMS, which is the sum of the emotional state subscales, was used. A higher TMD indicates greater emotional distress.

Psychiatric disorders

A trained psychiatrist (T.A.) conducted a Structured Clinical Interview based on the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition–revised [31] to evaluate major depression and adjustment disorders in each patient. In addition, the patients were asked to complete the Hospital Anxiety and Depression scale (HADS) at baseline. The HADS is a 14-item self-reported questionnaire consisting of an anxiety and depression subscale; the total score can range from 0 to 42 [32]. Higher scores indicate more severe depression and anxiety. The Japanese version of the HADS was validated in a cancer population, and the optimal cutoff point for screening for adjustment disorder and major depressive disorder was 10/11 [33].

Social support

The patients' use of confidants (number of confidants and satisfaction with confidants) was used as an indicator of social support factors. This information was obtained in a structured interview, as described previously [34]. In the interview, the patients were asked the number of people they had confided in since being diagnosed with cancer and how satisfied they were with their interactions with these confidants. When the patients had not confided in anyone, they were asked about their degree of satisfaction in not having done so. The patients' responses ranged from 1 to 7: 1, 'very dissatisfied'; 2, 'fairly dissatisfied'; 3, 'slightly dissatisfied'; 4, 'neither'; 5, 'somewhat satisfied'; 6, 'fairly satisfied'; and 7, 'very satisfied'.

Sociodemographic and biomedical factors

Sociodemographic factors (age, gender, marital status, education, household size, and employment status) were investigated using a structured interview at baseline. PS (assessed using the Eastern Cooperative Oncology Group criteria) was also investigated at baseline. In addition, the patient was asked about weight loss during the previous 6 months during the baseline interview. Blood laboratory tests (albumin level, hemoglobin level, leukocyte count, platelet count, and lactate dehydrogenase (LDH) level) were performed at the time of cancer diagnosis. (These biological factors were

evaluated because they are definite/possible prognostic factors for NSCLC, as mentioned above.) Information on clinical stage and anticancer treatment were obtained from the patients' charts. Smoking status and alcohol consumption were not assessed in the study.

Statistical analysis

Survival was defined as the interval between the date of the pathological diagnosis of lung cancer and the date of death or the date of the last follow-up information for surviving patients. Survival was examined at 2 years after the study enrollment period. In addition to the psychosocial factors, sex, ECOG PS, disease stage, histology, albumin level, hemoglobin level, leukocyte count, platelet count, LDH level, weight loss, and the use of chemotherapy were analyzed. These factors include all the definite and/or possible prognostic factors of NSCLC other than biologic factors, such as oncogenes (e.g. ras, p53, etc.). All factors except for sex, treatment factors, clinical stage, and PS were treated as continuous variables (clinical stage and PS were treated as ordinal variables) [35]. The survival curves were estimated according to the Kaplan–Meier method. Because the Kaplan–Meier analysis indicated that there were a total of 108 events (deaths), up to approximately 11 covariates could be entered into the regression analysis for prognostic prediction [36]. We investigated the correlation among psychosocial factors; when a statistically significant correlation with a correlation coefficient of over 0.30 was observed, more clinically relevant factors were retained. Correlation coefficients of over 0.30 were obtained for the following pairs: helplessness/hopelessness and TMD, helplessness/hopelessness and HADS, and HADS and satisfaction with confidants. We prioritized TMD and satisfaction with confidants from a clinical point of view. Finally, a total of five psychosocial factors (fighting spirit, TMD, major depression, number of confidants, and satisfaction with confidants) were chosen for further investigation. Regarding biomedical factors, two definite prognostic factors (PS and disease stage) were compulsorily entered for adjustment [24]. As for other possibly relevant biomedical factors, we investigated the correlations among the factors and if a statistically significant correlation with a correlation coefficient over 0.30 was observed, more clinically relevant factors were retained. Correlation coefficients of over 0.30 were obtained for the following pairs: leukocyte count and platelet count, hemoglobin level and platelet count, hemoglobin level and albumin level, and platelet count and albumin level. We prioritized hemoglobin from clinical point of view. Finally, a total of six biomedical factors (PS, disease stage, histology, hemoglobin, serum LDH,

and chemotherapy) were retained for further adjustment. Univariate and multivariate Cox proportional hazards regression models were used to determine the relationships between the investigated variables and survival. Biomedical and psychosocial variables that proved significant in the univariate analysis were simultaneously entered into the multivariate Cox regression, while PS and disease stage were compulsorily entered into the multivariate analysis regardless of the results of the univariate analysis. To explore the stability of the investigated psychosocial factors, except for the presence of the psychiatric diagnosis assessed by the psychiatric diagnostic interview, Pearson correlation coefficients or the concordance rate between T1 and T2 were investigated. A *P* value of less than 0.05 was adopted as the significance level in all of the statistical analyses, and all reported *P* values were two-tailed. All statistical procedures were conducted using the SPSS 10.0J version software for Windows (SPSS Inc., 2003).

Results

Characteristics of the participants

During the study entry period, 230 cases of unresectable NSCLC were newly diagnosed; 79 patients were found to be ineligible for enrollment in the study (brain metastasis, $n = 44$; illness too severe, $n = 16$; cognitive impairment, $n = 8$; active concomitant cancer, $n = 4$; not informed of the diagnosis, $n = 3$; PS of 3 or 4, $n = 3$; illiteracy, $n = 1$). Among the remaining 151 eligible patients, 21 patients refused to participate in the study and 8 patients could not be contacted; thus, 122 patients ultimately participated. No significant differences in age, sex, marital status, employment, histology, or clinical stage were observed between the participants ($n = 122$) and the non-participants ($n = 21$); however, the non-participants had significantly lower PSs than the participants ($P = 0.005$).

The patient characteristics are shown in Table 1. About half of the subjects were diagnosed as having stage IV lung cancer, and the overall median survival period was approximately 8.5 months. A total of six patients suffered from major depression. After a 2-year follow-up period, 108 patients had died. The survival data were censored for the remaining 14 patients.

A comparison of the survival of patients with various biomedical and psychosocial factors using a univariate analysis is shown in Table 2. Among the psychosocial factors, none of the investigated factors, including coping with cancer, psychological distress, psychiatric disorders, and social support, were significantly associated with

Table 1. Patient characteristics ($n = 122$)

		No (%)
Age (years)	Mean ± SD	62 ± 9
	Median (range)	64.5 (40–82)
Sex	Male	90 (74)
Marital status	Married	107 (88)
Education	< 10 y	62 (51)
Employment status	Full-time	34 (28)
	Part-time	5 (4)
	Housewife	15 (12)
	Retired	40 (33)
	Others	28 (23)
Household size	Living alone	8 (7)
Profile of Mood States	Mean ± SD	34.3 ± 33.3
(Total Mood Disturbance)	Median	27
Performance Status[a]	0	12 (10)
	1	104 (85)
	2	6 (5)
Histology	Adenocarcinoma	81 (64)
	Squamous cell	31 (25)
	Large cell	9 (7)
	Adenosquamous	1 (1)
Disease stage	III A	4 (3)
	III B	59 (48)
	IV	59 (48)
Survival (months)	Mean	11
	Median	8.6
	25 percentile	5.4
	75 percentile	15.2

[a]As defined by the Eastern Cooperative Oncology Group criteria.

Table 2. Comparison of the survival of patients with various biomedical and psychosocial factors—univariate Cox proportional regression analyses

Variable	Coefficient	SE	Hazards ratio (95% CI)	P
Performance Status[a]	0.49	0.31	1.63 (0.89–2.99)	0.11
Disease stage	0.36	0.19	1.43 (0.99–2.07)	0.06
Histology (squamous cell)	0.34	0.22	1.40 (0.91–2.16)	0.13
Hemoglobin (g/dl)	−0.09	0.05	0.92 (0.83–1.02)	0.11
Serum LDH (IU/l)	0.001	0.000	1.001 (1.000–1.001)	0.001
Treatment (CTx)	−0.50	0.23	0.61 (0.39–0.96)	0.03
Fighting spirit[b]	0.02	0.02	1.02 (0.99–1.05)	0.16
Total Mood Disturbance[c]	0.002	0.003	1.002 (0.996–1.01)	0.53
Major depression	−0.23	0.46	0.79 (0.32–1.95)	0.61
Number of confidants	−0.01	0.02	0.99 (0.96–1.03)	0.71
Satisfied with confidant	−0.01	0.08	0.99 (0.84–1.16)	0.87

Psychosocial factors were assessed at after diagnosis but before treatment.
CI: confidence interval; LDH: lactate dehydrogenase; CTx: chemotherapy.
[a]As defined by the Eastern Cooperative Oncology Group criteria.
[b]Mental Adjustment Cancer Scale.
[c]Profile of mood states.

the survival period. Among the biomedical factors, a higher serum LDH level and not receiving chemotherapy were significantly associated with shorter survival periods.

Table 3. Multivariate Cox proportional regression analysis

Variable	Coefficient	SE	Hazards ratio (95% CI)	P
Performance Status[a]	0.30	0.31	1.35 (0.74–2.48)	0.33
Disease stage	0.41	0.19	1.50 (1.03–2.19)	0.04
Serum LDH (IU/L)	0.001	0.000	1.001 (1.000–1.001)	0.001
Treatment (CTx)	−0.54	0.24	0.59 (0.37–0.93)	0.03

CI: confidence interval; LDH: lactate dehydrogenase; CTx: chemotherapy.
[a]As defined by the Eastern Cooperative Oncology Group criteria.

A multivariate Cox proportional regression analysis indicated that an advanced clinical stage, a higher serum LDH level, and not receiving chemotherapy were independently associated with a shorter survival period among patients with inoperable NSCLC (Table 3). In addition, we preliminarily conducted a stepwise Cox regression analysis (backward elimination), including the aforementioned five psychosocial factors and six biomedical factors. The findings also indicated that advanced disease stage, a high LDH level, and no chemotherapy were significantly associated with a shorter survival period (data not shown).

Regarding the stability of the psychosocial factors, our findings demonstrated that the correlation coefficients of the fighting spirit subscale of the MAC, the TMD of the POMS, the number of confidants, and the satisfaction with the confidants between T1 and T2 were 0.65 ($P<0.001$), 0.54 ($P<0.001$), 0.45 ($P<0.001$), and 0.18 ($P=0.06$), respectively. These findings suggested a moderate to high stability of most of the psychosocial factors other than the perceived satisfaction with social support.

Discussion

This is the first prospective cohort study to clarify the association between a broad range of psychosocial factors and survival among homogenous patients with advanced NSCLC. The present study has several advantages. First, we assessed most of the well-established biomedical prognostic factors, although the final analysis did not need to adjust for these factors. Second, we first investigated clinical depression using the most reliable method available (a structured clinical interview conducted by a trained psychiatrist). Third, we ascertained the stability of the psychosocial factors subsequent to the cancer diagnosis.

Our results demonstrated that psychosocial factors, including coping with cancer, psychological distress, clinical depression, and social support, are not significantly associated with survival time among inoperable patients with NSCLC. Overall, the findings that a specific coping style, 'fighting spirit', and clinical depression

had no significant effect on survival in advanced lung cancer patients should be emphasized because it is commonly believed that a patient's coping with cancer and negative emotions, especially depression, can affect his or her chances of surviving cancer. In addition, because our study confirmed the moderate to high stability of several of the psychosocial factors, we found little convincing evidence that a weak 'fighting spirit' or negative emotions after cancer diagnosis played a clinically relevant role in survival from cancer, even when these findings were stable over relatively long periods of time. Furthermore, our study demonstrates that social support factors do not have an important influence on survival time among advanced lung cancer patients. These findings are consistent with some previous studies and our findings suggest that advanced lung cancer patients need not feel pressured into adopting a specific coping style to cancer or blame themselves for having 'negative emotions and/or depression' after their cancer diagnosis that might affect their survival [37,38]. The present findings may be relevant because the psychological distress experienced by lung cancer patients has been repeatedly reported to be higher than in other cancer patients (see Introduction). Furthermore, this study provides the first findings about clinically diagnosed depression, namely major depression, after a diagnosis of inoperable lung cancer and the subsequent survival time. Although many previous studies have demonstrated a significant association between depression and survival among cancer patients [28,39,40] and patients with other diseases, especially cardiovascular patients [41,42], the current findings are not consistent with the previous findings. This may be partly due to the differences in the subjects and the relatively small sample size (e.g. only six patients suffered from major depression). Further, large studies may be needed to obtain more conclusive findings between clinical depression and survival among lung cancer patients.

Finally, we would like to mention a possible effect of Japanese culture on the findings obtained. In Japan, a diagnosis of cancer is still often considered to be the equivalent of a death sentence, and the disclosure of a cancer diagnosis is not universally practiced [43]. Although the institution at which the present study was conducted is exceptional in that a cancer diagnosis is usually disclosed to the patient, cultural differences in patient–physician communication and the social meaning of a cancer diagnosis may have influenced the psychosocial factors that were investigated and be consequently may be somewhat associated with the present findings. In addition, previous Japanese studies have consistently indicated a somewhat lower prevalence of major depression, ranging between 4 and 7%, among cancer patients,

compared with findings from Western countries [12,44–46]. Thus, the low prevalence of major depression is unlikely to represent a sampling bias, but rather cultural differences—as discussed in our previous study [12,46].

We would like to emphasize that our findings do not imply that dealing with psychosocial issues among cancer patients in clinical oncology setting is unimportant. As many studies have indicated, psychosocial issues not only cause serious suffering [47], but also worsen the quality of life [48], reduces compliance with anticancer treatment [49], can lead to suicide [50], are a psychological burden on the family [51], and prolongs hospitalization [52].

Although it was not the principal purpose of our study, we would like to note that our findings suggest that the serum LDH level could be a useful independent biomedical prognostic factor of the length of survival among patients with advanced NSCLC. LDH is an enzyme that is released into the peripheral blood after cell death. Therefore, the serum LDH level may represent biomedical conditions associated with the length of survival among patients with advanced NSCLC. A rigorous psycho-oncological study investigating the influence of psychosocial factors on survival may be needed to evaluate these biomedical factors as well as psychosocial factors.

Our study also has some weaknesses. First, since only 53.0% (122/230) of the subjects could be included in the analysis, generalizing the results may be problematic, and the sample size of the follow-up group was not very large. Second, the fact that the patients who participated in the study were more likely to have a better PS than those who did not indicate a potential selection bias. Third, as mentioned above, because the number of cases with clinical depression was quite small, the validity of our findings regarding the association between clinical depression and survival may be limited. To overcome these limitations, we are conducting a large-scale cohort study involving more than 2000 subjects to investigate psychosocial factors and survival among lung cancer patients [53]. Since the present study was conducted at one institution, an institutional bias may be another problem. Because current smoking at the time of lung cancer diagnosis could be an independent predictor of survival and a close association between smoking and emotional distress has been documented [54,55], the lack of data on continuous tobacco use after cancer diagnosis and its relationship with emotional distress and survival may be an additional limitation. Finally, because this study focused on advanced NSCLC cancer patients, the results may not be applicable to patients with other types and/or clinical stages of cancer.

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